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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/055,711	REBAR ET AL.
	Examiner	Art Unit
	Jennifer Dunston	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,23-28,30-48,52-57 and 62-64* is/are pending in the application.

4a) Of the above claim(s) *1,23,24,33-35,38,42-48 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28,30-32,36,37,39-41,53-57 and 62-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/9/2011 has been entered.

Receipt is acknowledged of an amendment, filed 5/9/2011, in which claim 30 was amended, and claims 62-64 were amended. Claims 1, 23-28, 30-48, 52-57 and 62-64 are pending.

Election/Restrictions

Applicant elected Group II (drawn to nucleic acid), species: DNA target sequence, zinc finger component comprising X(3)-Cys-X(2)-Cys-X(12)-His-X(3)-Z-X(4), target located in a plant cell, and a maize C1 activation domain in the replies filed on 8/3/2004 and 11/18/2004. This restriction requirement was made FINAL in the Office action mailed 2/9/2005 and reiterated in the Office action mailed 11/15/2005.

The requirement for the election of a specific zinc finger component, as set forth on pages 3-4 of the Office action mailed 7/1/2004 was withdrawn in the Office action mailed 6/14/2206. The remainder of the species election requirement was maintained in the Office action mailed

6/14/2006. Thus, the species election requirements for target sequence type (DNA), where the target is located (plant cell), and functional domain type (C1 activation domain) are maintained.

Claims 1, 33, 42-48 and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Claims 23-24, 34-35 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Currently, claims 25-28, 30-32, 36-37, 39-41, 53-57 and 62-64 are under consideration.

Claim Objections

Claim 56 is objected to because of the following informalities: the word "residues" should be added after the word "cysteine" in line 5 of the claim to improve the grammar. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 25-28, 30-32, 36, 37, 39-41, 53-57 and 62-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 23 of copending Application No. 12/001,939 (hereinafter the '939 application) in view of Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action), and Desjarlais et al (Proceedings of the National Academy of Sciences, USA, Vol. 90, No. 6, pages 2256-2260, March 1993, cited as reference C38 on the IDS filed 5/11/2005; see the entire reference). This is a new rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a polynucleotide encoding a non-naturally occurring zinc finger protein comprising a non-canonical zinc finger component. Specifically, claim 23 of the '939 application is drawn to a polynucleotide encoding a zinc finger protein comprising a non-canonical (non-C2H2) zinc finger, wherein the non-canonical zinc finger has a helical portion involved in DNA binding and wherein at least one zinc finger comprises the sequence Cys-$(X^A)_{2-4}$-Cys-$(X^B)_{12}$-His-$(X^C)_{3-5}$-Cys-$(X^D)_{1-10}$, where X^A, X^B, X^C and X^D can be any amino acid and wherein (i) the zinc finger protein is engineered to bind to a target sequence; (ii) $(X^D)_{1-10}$ comprises an amino acid sequence selected from the group consisting of QKP, QVL, and a G residue immediately C-terminal to the C-terminal Cys residue; and (iii) if $(X^D)_{1-10}$ comprises the amino acid sequence QKP and $(X^C)_{3-5}$ consists of 3 amino acids, the residues of $(X^C)_3$ are selected from the group consisting of IRT, IRR, TKI and AQR. Thus, claim 23 of the '939 application anticipates instant claims 30, 56 and 57 of the instant application. The claims of the '969 application do not recite each of the limitations of the dependent claims of the present application. However, each limitation would have been obvious based upon the teachings of Barbas, III et al. Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). The region of the zinc finger protein that mediates the specific binding spans positions -1 to +6 of the alpha helix and, thus, is a recognition helix of seven amino acids in length (e.g., column 21, lines 34-39; boxed sequences in Figure 6). Barbas, III et

al teach that any naturally occurring zinc finger protein can be used as a framework (or backbone) to derive a non-naturally occurring zinc finger with DNA binding specificity determined by alterations in the alpha helix using known design rules (e.g., column 5, lines 6-11; column 10, lines 55-67; column 11, lines 14-35; column 19, lines 28-34 and 53-57; column 21, lines 8-39; column 22, line 51 to column 25, line 9). Barbas, III et al teach that any suitable method known in the art can be used to design and construct nucleic acids encoding zinc finger polypeptides, including the use of PCR and ligation (e.g., column 20, lines 15-40). Barbas, III et al teach that the use of PCR primers that encode a finger sequence or part thereof with known base pair specificity, and that can be reused or recombined to create new combinations of fingers and zinc finger protein sequences is preferred for cost and flexibility (e.g., column 20, lines 36-40). Barbas, III et al teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Further, Barbas III et al teach that the target nucleotide sequence can be endogenous or exogenous to the target gene (e.g., column 3, lines 23-50). Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36). Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67). It would have been obvious to one of ordinary skill in the art to link together the nucleic acid binding domain

and a heterologous C1 activation domain, provide the sequence in an expression vector, provide a composition comprising the vector and a pharmaceutically acceptable excipient, and provide an isolated plant host cell comprising the vector in order to achieve the predictable result of providing a cell capable of expressing the encoded zinc finger polypeptide for regulation of gene expression in the plant cell. Furthermore, the claims of the '939 application do not specify the K and F residues of present claims 62 and 63. However, Desjarlais et al teach the use of these residues at the claimed positions. It would have been obvious to one of ordinary skill in the art to use these particular residues, because the claims of the '939 application indicate that X may be any amino acid. One would have been motivated to use the residues of Desjarlais et al in order to use residues known to provide the proper function of the zinc finger domain.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56 and 57 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action; see the entire reference) in view of Filippova et al (Molecular and Cellular Biology, Vol. 16, No. 6, pages 2802-2813, June 1996; see the entire reference). This rejection was made in the Office action mailed 4/27/2009.

The rejection is maintained for the reasons of record, including the affirmation of the rejection by the Board of Patent Appeals and Interferences on 3/10/2011.

Claims 56 and 57 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,329,728 B1; see the entire reference) in view of Filippova et al (Molecular and Cellular Biology, Vol. 16, No. 6, pages 2802-2813, June 1996; see the entire reference). This rejection was made in the Office action mailed 4/27/2009.

The rejection is maintained for the reasons of record, including the affirmation of the rejection by the Board of Patent Appeals and Interferences on 3/10/2011.

Claims 25-28, 30-32, 36-37, 39-41, 53-57 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action; see the entire reference) in view of Desjarlais et al (Proceedings of the National Academy of Sciences, USA, Vol. 90, No. 6, pages 2256-2260, March 1993, cited as reference C38 on the IDS

filed 5/11/2005; see the entire reference), Krizek et al (Journal of the American Chemical Society, Vol. 113, pages 4518-4523, 1991; see the entire reference), and Roehm et al (Journal of the American Chemical Society, Vol. 120, pages 13083-13087, 1998; see the entire reference). This is a new rejection, necessitated by the amendment to independent claim 30 and the addition of new claims 62-64 in the reply filed 5/9/2011.

Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). The region of the zinc finger protein that mediates the specific binding spans positions -1 to +6 of the alpha helix and, thus, is a recognition helix of seven amino acids in length (e.g., column 21, lines 34-39; boxed sequences in Figure 6). Barbas, III et al teach that any naturally occurring zinc finger protein can be used as a framework (or backbone) to derive a non-naturally occurring zinc finger with DNA binding specificity determined by alterations in the alpha helix using known design rules (e.g., column 5, lines 6-11; column 10, lines 55-67; column 11, lines 14-35; column 19, lines 28-34 and 53-57; column 21, lines 8-39; column 22, line 51 to column 25, line 9). Barbas, III et al teach that any suitable method known in the art can be used to design and construct nucleic acids encoding zinc finger polypeptides, including the use of PCR and ligation (e.g., column 20, lines 15-40). Barbas, III et al teach that the use of PCR primers that encode a finger sequence or part thereof with known base pair specificity, and that can be reused or recombined to create new combinations of fingers and zinc finger protein sequences is preferred for cost and flexibility (e.g., column 20, lines 36-40). Barbas, III et al

teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Further, Barbas III et al teach that the target nucleotide sequence can be endogenous or exogenous to the target gene (e.g., column 3, lines 23-50). Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36). Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating cysteine residues separated by two amino acids and an alpha helix comprising one carboxy-terminal zinc coordinating histidine residue and one carboxy-terminal cysteine residue, where the carboxy-terminal histidine residue is amino terminal to the carboxy-terminal cysteine residue and the histidine and cysteine residues are separated by three amino acids, where at least one of the residues in this region is altered as compared to a naturally-occurring zinc finger.

Desjarlais et al teach a polynucleotide encoding a consensus sequence framework for zinc-finger protein design, where the framework comprises three copies of a CP-1 consensus sequence, where the alpha helical regions were engineered to change the target nucleotide

sequence specificity of the protein (e.g., Results and Discussion at pages 2257-2260; Figure 1). Desjarlais et al teach a general scheme for the construction of a polynucleotide encoding tandem zinc finger arrays, the scheme comprising a stepwise subcloning approach, which makes use of *Xma* I and *Cfr*10I restriction sites which, when ligated together, yield a hybrid site that is no longer cleavable by either enzyme (e.g., Figure 2). Because the hybrid site is not cleavable, the ligated fragment is suitable for another round of zinc-finger addition (e.g., Figure 2). Desjarlais et al teach that it is possible to design functional zinc-finger proteins based on multiple consensus-based zinc-finger motifs with appropriate changes endowing specificity to the individual zinc fingers and teach that this system should prove to be a powerful vehicle for the production of desired site-specific DNA binding proteins (e.g., page 2260, paragraph bridging columns).

Krizek et al teach that a large class of proteins has been discovered that is characterized by the presence of one or more sequences that closely approximate the form (Tyr,Phe)-X-Cys-$X_{2,4}$-Cys-X_3-Phe-X_5-Leu-X_2-His-$X_{3,4}$ where X represents relatively variable amino acids and where the structure fold into unique three-dimensional structures in the presence of metal ions (e.g., page 4518, left column, 1st paragraph). Krizek et al teach that the structure comprises a beta turn comprising two amino terminal zinc coordinating residues, and an alpha helix comprising two carboxy-terminal zinc coordinating residues (e.g., Figures 1 and 2). Krizek et al teach that a total of 131 sequences were known at the time their project was initiated, and the sequences are tabulated in Table 1 (e.g., page 4518, left column, 2nd paragraph). These sequences were used to construct a consensus zinc finger peptide, where the sequence of the peptide was determined by selecting the amino acid that occurred in the large number of zinc

finger domains at each position (e.g., page 4519, paragraph bridging columns). The sequence of the consensus peptide (hereafter CP-1) is

ProTyrLys**Cys**ProGlu**Cys**GlyLysSerPheSerGlnLysSerAspLeuValLys**His**GlnArgThr**His**ThrGly

(e.g., page 4519, paragraph bridging columns). This sequence comprises substitutions of the amino acids between the amino terminal zinc coordinating and carboxy terminal zinc coordinating residues and between the two terminal zinc coordinating residues relative to the sequences shown in Table 1 of Krizek et al. Krizek et al teach that examination of the sequence database revealed that six of the sequences lack the final histidine residue but have a cysteine residue within five amino acids of the conserved histidine (e.g., paragraph bridging pages 4521-4522). Krizek et al teach that this observation suggested that cysteine could replace histidine as a metal-binding ligand from this position (e.g., paragraph bridging pages 4521-4522). Based upon these observations, Krizek et al created a sequence variant of CP-1, where the final histidine in the consensus sequence was replaced with cysteine (CP-1 H24C; e.g., paragraph bridging pages 4521-4522). Krizek et al teach that the H24C variant of CP-1 also bound metal ions (e.g., page 4523, paragraph bridging columns).

Roehm et al teach that the second histidine of the zinc finger structure can be substituted with cysteine without significant loss of structure or stability (e.g., Abstract). Roehm et al teach that the cysteine at position 24 of CP-1 H24C has more space available to accommodate structure changes as indicated by the lack of substantial differences in metal binding properties following substitution of histidine or cysteine at this position (e.g., page 13087, right column, full paragraph).

Because Barbas, III et al disclose nucleic acid molecules encoding a zinc finger protein comprising a zinc finger domain from any naturally occurring protein that has been used as a framework for modifying the DNA binding specificity of the alpha helix according to known design rules, and Desjarlais et al teach nucleic acid molecules encoding a consensus zinc finger protein sequence as a framework for modifying the DNA binding specificity of the alpha helix according to the binding specificities of known proteins, it would have been obvious to one of ordinary skill in the art to substitute a nucleic acid sequence consensus zinc finger framework protein sequence of Desjarlais in place of the naturally occurring protein sequence framework of Barbas, III et al in order to achieve the predictable result of providing a nucleic acid molecule encoding a protein comprising multiple zinc finger domains capable of binding to a target nucleic acid sequence in a plant cell. The protein sequence framework of Desjarlais et al has two amino terminal zinc coordinating cysteine residues separated by two amino acids, and carboxy terminal histidine residues separated by three amino acids, where the amino acids between the two carboxy terminal zinc coordinating residues have been substituted relative to wild type proteins. The sequence falls within the consensus sequence of instant claims 62-63. One would have been motivated to make such a modification, because Desjarlais et al teach that the consensus system should prove to be a powerful vehicle for the production of desired site-specific DNA binding proteins.

Furthermore, it would have been obvious to one of ordinary skill in the art to modify the combined teachings of Barbas, III et al and Desjarlais et al to substitute the polynucleotides encoding the CP-1 consensus sequence with a polynucleotide encoding the CP-1 H24C consensus sequence of Krizek et al, because Krizek et al teach that similar sequence are found in

known zinc finger-DNA binding proteins, such as Drosophila Snail (e.g., Table I), and because Roehm et al teach that the CP-1 H24C variant has essentially the same structure and metal binding properties as the CP-1 variant. Thus, one would have a reasonable expectation of success in substituting the CP-1 H24C variant for any one of fingers 1, 2 and/or 3 in the protein encoded by the polynucleotide of Barbas, III et al and Desjarlais et al in order to obtain a polynucleotide encoding a site-specific DNA binding protein. One would have been motivated to make such a modification in order to expand the repertoire of polynucleotides encoding engineered zinc finger polypeptides.

Claims 25-28, 30-32, 36-37, 39-41, 53-57 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action; see the entire reference) in view of Krizek et al (Journal of the American Chemical Society, Vol. 113, pages 4518-4523, 1991; see the entire reference), and Boulay et al (Nature, Vol. 330, pages 395-398, November 1987; see the entire reference). This is a new rejection, necessitated by the amendment to independent claim 30 and the addition of new claims 62-64 in the reply filed 5/9/2011.

Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). The region of the zinc finger protein that mediates the specific binding spans positions -1 to +6 of the alpha helix and, thus, is a recognition helix of seven amino acids

in length (e.g., column 21, lines 34-39; boxed sequences in Figure 6). Barbas, III et al teach that any naturally occurring zinc finger protein can be used as a framework (or backbone) to derive a non-naturally occurring zinc finger with DNA binding specificity determined by alterations in the alpha helix using known design rules (e.g., column 5, lines 6-11; column 10, lines 55-67; column 11, lines 14-35; column 19, lines 28-34 and 53-57; column 21, lines 8-39; column 22, line 51 to column 25, line 9). Barbas, III et al teach that the individual zinc finger domains are linked with a linker region from about 2 to about 10 amino acids in length, preferably about 5 amino acids, after the C-terminal zinc coordinating residue (e.g., column 4, line 59 to column 5, line 3; claims 20-21). Barbas, III et al teach that any suitable method known in the art can be used to design and construct nucleic acids encoding zinc finger polypeptides, including the use of PCR and ligation (e.g., column 20, lines 15-40). Barbas, III et al teach that the use of PCR primers that encode a finger sequence or part thereof with known base pair specificity, and that can be reused or recombined to create new combinations of fingers and zinc finger protein sequences is preferred for cost and flexibility (e.g., column 20, lines 36-40). Barbas, III et al teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Further, Barbas III et al teach that the target nucleotide sequence can be endogenous or exogenous to the target gene (e.g., column 3, lines 23-50). Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g.,

column 32, lines 10-36). Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating cysteine residues separated by two amino acids and an alpha helix comprising one carboxy-terminal zinc coordinating histidine residue and one carboxy-terminal cysteine residue, where the carboxy-terminal histidine residue is amino terminal to the carboxy-terminal cysteine residue and the histidine and cysteine residues are separated by four amino acids, and where four amino acids are added C-terminal to the carboxy-terminal zinc coordinating residue.

Krizek et al teach that a large class of proteins has been discovered that is characterized by the presence of one or more sequences that closely approximate the form (Tyr,Phe)-X-Cys-$X_{2,4}$-Cys-X_3-Phe-X_5-Leu-X_2-His-$X_{3,4}$ where X represents relatively variable amino acids and where the structure fold into unique three-dimensional structures in the presence of metal ions (e.g., page 4518, left column, 1st paragraph). Krizek et al teach that the structure comprises a beta turn comprising two amino terminal zinc coordinating residues, and an alpha helix comprising two carboxy-terminal zinc coordinating residues (e.g., Figures 1 and 2). Krizek et al teach that a total of 131 sequences were known at the time their project was initiated, and the sequences are tabulated in Table 1 (e.g., page 4518, left column, 2nd paragraph). Krizek et al teach that examination of the sequence database revealed that six of the sequences lack the final histidine residue but have a cysteine residue within five amino acids of the conserved histidine

(e.g., paragraph bridging pages 4521-4522). One such sequence is KYA**C**QV**C**HKSFSRMSLLNK**H**SSSN**C**TI from Drosophila Snail (e.g., Table 1). This sequence has two amino acids separating the two amino terminal zinc coordinating cysteine residues, and four amino acids separating the two carboxy-terminal zinc coordinating histidine and cysteine residues. Krizek et al teach that observation of zinc finger domains with a terminal cysteine suggested that cysteine could replace histidine as a metal-binding ligand from this position (e.g., paragraph bridging pages 4521-4522).

Boulay et al teach a polynucleotide encoding the KYA**C**QV**C**HKSFSRMSLLNK**H**SSSN**C**TI zinc finger of Drosophila Snail (e.g., Figure 3). Boulay et al teach that the Snail protein belongs to the class of regulatory proteins with DNA-binding activity (e.g., Title; page 397, right column; paragraph bridging pages 397-398).

Because Barbas, III et al disclose nucleic acid molecules encoding a zinc finger protein comprising a zinc finger domain from any naturally occurring protein that has been used as a framework for modifying the DNA binding specificity according to known design rules, and Boulay et al teach a nucleic acid molecule encoding a zinc finger protein that binds DNA, it would have been obvious to one or ordinary skill in the art at the time the invention was made to include the framework sequence encoding the last finger (i.e., the CCHC zinc finger) of the Drosophila Snail protein, as shown by Krizek et al and Boulay et al, in the nucleic acid molecules of Barbas, III et al, where the finger of the Snail protein sequence has been modified to include a recognition helix that is engineered to bind the a target nucleic acid sequence taught by Barbas, III et al, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing the target nucleic acid

sequence of Barbas, III et al. With respect to claims 28 and 54, which require the non-canonical zinc finger component to be the third zinc finger component or the first zinc finger component, respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the zinc fingers of Barbas III et al and Boulay et al in an order from N-terminus to C-terminus such that the non-canonical zinc fingers are present at the first and/or third zinc fingers. However, it is noted that the claims do not explicitly impose a linear order to the first, second and third zinc fingers. With respect to claims 62 and 63, the non-canonical zinc finger encoded by the polynucleotide based upon the Drosophila Snail framework would fall within the scope of the sequence of claim 62. Furthermore, Krizek et al teach that there are typically 3-4 amino acids C-terminal to the carboxy-terminal zinc coordinating residue, and Barbas, III et al teach linkage of zinc finger domains with about 5 amino acids. Thus, it would have been obvious to one of ordinary skill in the art to include 4 amino acids C-terminal to the carboxy-terminal zinc coordinating residue in order to provide a complete zinc finger domain linked to another zinc finger domain.

Furthermore, one would have been motivated to include the sequence encoding the CCHC type zinc fingers of Krizek et al and Boulay et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 25-28, 30-32, 36, 39-41, 53-57 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,329,728 B1; see the entire reference) in view of Desjarlais et al (Proceedings of the National Academy of Sciences, USA, Vol. 90, No. 6, pages 2256-2260, March 1993, cited as reference C38 on the IDS filed 5/11/2005; see the entire reference), Krizek et al (Journal of the American Chemical Society, Vol. 113, pages 4518-4523, 1991; see the entire reference), and Roehm et al (Journal of the American Chemical Society, Vol. 120, pages 13083-13087, 1998; see the entire reference). This is a new rejection, necessitated by the amendment to independent claim 30 and the addition of new claims 62-64 in the reply filed 5/9/2011.

Barbas, III et al teach nucleic acid molecules encoding fusion proteins, expression vectors containing the nucleic acids, and cells containing the expression vectors, where the cells are plant cells (e.g., column 2, lines 18-24; column 3, lines 12-14). Further, Barbas, III et al teach compositions comprising the nucleic acid molecule and a pharmaceutically acceptable excipient (e.g., column 5, lines 49-56). Barbas, III et al teach that the fusion protein encoded by the nucleic acid molecule includes at least one DNA binding domain, at least one ligand binding domain, and at least one transcription modulating domain, and regulates expression by binding to a target sequence in a promoter (e.g., column 2, lines 59-67; column 5, line 66 to column 6, line 22; column 9, lines 56-60; column 17, lines 41-50; paragraph bridging columns 17-18). The transcription modulating domain may be a transcription activation domain (e.g., column 29, lines 30-34). In a preferred embodiment, the DNA binding domain includes at least three zinc finger modular units and binds to at least nine nucleotides (e.g., paragraph bridging columns 2-3; column 3, lines 59-64; paragraph bridging columns 20-21). For example, six zinc fingers will

bind to a sequence of 18-bp (e.g., paragraph bridging columns 20-21). Barbas, III et al teach that it is advantageous to use zinc fingers, because of the ability to construct zinc fingers with unique specificity, which permits targeting and ligand-dependent control of expression of specific endogenous genes or exogenously administered genes (e.g., column 19, lines 28-35). Barbas, III et al teach that rules for creating synthetic zinc fingers with specificity to any desired target sequence are known (e.g., column 19, lines 36-49). Barbas, III et al teach that a zinc finger-nucleotide binding peptide domain contains a unique heptamer within the alpha-helical domain of the polypeptide, which heptameric sequence determines the binding specificity to the target nucleotide (e.g., column 20, lines 43-53). Further, Barbas, III et al teach that any framework sequences known in the art to function as part of a zinc finger protein can be modified to include a peptide nucleotide-binding domain (e.g., column 20, line 43 to column 21, line 20).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating cysteine residues separated by two amino acids and an alpha helix comprising one carboxy-terminal zinc coordinating histidine residue and one carboxy-terminal cysteine residue, where the carboxy-terminal histidine residue is amino terminal to the carboxy-terminal cysteine residue and the histidine and cysteine residues are separated by three amino acids, where at least one of the residues in this region is altered as compared to a naturally-occurring zinc finger.

Desjarlais et al teach a polynucleotide encoding a consensus sequence framework for zinc-finger protein design, where the framework comprises three copies of a CP-1 consensus sequence, where the alpha helical regions were engineered to change the target nucleotide

sequence specificity of the protein (e.g., Results and Discussion at pages 2257-2260; Figure 1). Desjarlais et al teach a general scheme for the construction of a polynucleotide encoding tandem zinc finger arrays, the scheme comprising a stepwise subcloning approach, which makes use of *Xma* I and *Cfr*10I restriction sites which, when ligated together, yield a hybrid site that is no longer cleavable by either enzyme (e.g., Figure 2). Because the hybrid site is not cleavable, the ligated fragment is suitable for another round of zinc-finger addition (e.g., Figure 2). Desjarlais et al teach that it is possible to design functional zinc-finger proteins based on multiple consensus-based zinc-finger motifs with appropriate changes endowing specificity to the individual zinc fingers and teach that this system should prove to be a powerful vehicle for the production of desired site-specific DNA binding proteins (e.g., page 2260, paragraph bridging columns).

Krizek et al teach that a large class of proteins has been discovered that is characterized by the presence of one or more sequences that closely approximate the form (Tyr,Phe)-X-Cys-$X_{2,4}$-Cys-X_3-Phe-X_5-Leu-X_2-His-$X_{3,4}$ where X represents relatively variable amino acids and where the structure fold into unique three-dimensional structures in the presence of metal ions (e.g., page 4518, left column, 1st paragraph). Krizek et al teach that the structure comprises a beta turn comprising two amino terminal zinc coordinating residues, and an alpha helix comprising two carboxy-terminal zinc coordinating residues (e.g., Figures 1 and 2). Krizek et al teach that a total of 131 sequences were known at the time their project was initiated, and the sequences are tabulated in Table 1 (e.g., page 4518, left column, 2nd paragraph). These sequences were used to construct a consensus zinc finger peptide, where the sequence of the peptide was determined by selecting the amino acid that occurred in the large number of zinc

finger domains at each position (e.g., page 4519, paragraph bridging columns). The sequence of the consensus peptide (hereafter CP-1) is ProTyrLys**Cys**ProGlu**Cys**GlyLysSerPheSerGlnLysSerAspLeuValLys**His**GlnArgThr**His**ThrGly (e.g., page 4519, paragraph bridging columns). This sequence comprises substitutions of the amino acids between the amino terminal zinc coordinating and carboxy terminal zinc coordinating residues and between the two terminal zinc coordinating residues relative to the sequences shown in Table 1 of Krizek et al. Krizek et al teach that examination of the sequence database revealed that six of the sequences lack the final histidine residue but have a cysteine residue within five amino acids of the conserved histidine (e.g., paragraph bridging pages 4521-4522). Krizek et al teach that this observation suggested that cysteine could replace histidine as a metal-binding ligand from this position (e.g., paragraph bridging pages 4521-4522). Based upon these observations, Krizek et al created a sequence variant of CP-1, where the final histidine in the consensus sequence was replaced with cysteine (CP-1 H24C; e.g., paragraph bridging pages 4521-4522). Krizek et al teach that the H24C variant of CP-1 also bound metal ions (e.g., page 4523, paragraph bridging columns).

Roehm et al teach that the second histidine of the zinc finger structure can be substituted with cysteine without significant loss of structure or stability (e.g., Abstract). Roehm et al teach that the cysteine at position 24 of CP-1 H24C has more space available to accommodate structure changes as indicated by the lack of substantial differences in metal binding properties following substitution of histidine or cysteine at this position (e.g., page 13087, right column, full paragraph).

Because Barbas, III et al disclose nucleic acid molecules encoding a zinc finger protein comprising a zinc finger domain from any naturally occurring protein that has been used as a framework for modifying the DNA binding specificity of the alpha helix according to known design rules, and Desjarlais et al teach nucleic acid molecules encoding a consensus zinc finger protein sequence as a framework for modifying the DNA binding specificity of the alpha helix according to the binding specificities of known proteins, it would have been obvious to one of ordinary skill in the art to substitute a nucleic acid sequence consensus zinc finger framework protein sequence of Desjarlais in place of the naturally occurring protein sequence framework of Barbas, III et al in order to achieve the predictable result of providing a nucleic acid molecule encoding a protein comprising multiple zinc finger domains capable of binding to a target nucleic acid sequence in a plant cell. The protein sequence framework of Desjarlais et al has two amino terminal zinc coordinating cysteine residues separated by two amino acids, and carboxy terminal histidine residues separated by three amino acids, where the amino acids between the two carboxy terminal zinc coordinating residues have been substituted relative to wild type proteins. The sequence falls within the consensus sequence of instant claims 62-63. One would have been motivated to make such a modification, because Desjarlais et al teach that the consensus system should prove to be a powerful vehicle for the production of desired site-specific DNA binding proteins.

Furthermore, it would have been obvious to one of ordinary skill in the art to modify the combined teachings of Barbas, III et al and Desjarlais et al to substitute the polynucleotides encoding the CP-1 consensus sequence with a polynucleotide encoding the CP-1 H24C consensus sequence of Krizek et al, because Krizek et al teach that similar sequence are found in

known zinc finger-DNA binding proteins, such as Drosophila Snail (e.g., Table I), and because Roehm et al teach that the CP-1 H24C variant has essentially the same structure and metal binding properties as the CP-1 variant. Thus, one would have a reasonable expectation of success in substituting the CP-1 H24C variant for any one of fingers 1, 2 and/or 3 in the protein encoded by the polynucleotide of Barbas, III et al and Desjarlais et al in order to obtain a polynucleotide encoding a site-specific DNA binding protein. One would have been motivated to make such a modification in order to expand the repertoire of polynucleotides encoding engineered zinc finger polypeptides.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,329,728 B1; see the entire reference) in view of Desjarlais et al (Proceedings of the National Academy of Sciences, USA, Vol. 90, No. 6, pages 2256-2260, March 1993, cited as reference C38 on the IDS filed 5/11/2005; see the entire reference), Krizek et al (Journal of the American Chemical Society, Vol. 113, pages 4518-4523, 1991; see the entire reference), and Roehm et al (Journal of the American Chemical Society, Vol. 120, pages 13083-13087, 1998; see the entire reference) as applied to claims 25-28, 30-32, 36, 39-41, 53-57 and 62-64 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of claim 30 in the reply filed 5/9/2011.

The combined teachings of Barbas, III et al, Desjarlais et al, Krizek et al, and Roehm et al are described above and applied as before.

Barbas, III et al, Desjarlais et al, Krizek et al, and Roehm et al do not teach the polynucleotide where the activation domain is a maize C1 activation domain.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and activatable transgene are brought together in the same cell by fertilization (e.g. paragraph bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g. paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al because Barbas, III et al teach it is within the skill of the art to make a plant cell comprising the polynucleotide where the polynucleotide encodes a zinc finger-nucleotide binding polypeptide that activates expression of a gene operably linked to the target nucleotide sequence, and Guyer et al teach that the maize C1 activation domain functions in a plant cell to activate transcription from a heterologous DNA binding domain.

One would have been motivated to specifically use the maize C1 activation domain, because it was known in the art to function in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 25-28, 30-32, 36, 39-41, 53-57 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,329,728 B1; see the entire reference) in view of Krizek et al (Journal of the American Chemical Society, Vol. 113, pages 4518-4523, 1991; see the entire reference), and Boulay et al (Nature, Vol. 330, pages 395-398, November 1987; see the entire reference). This is a new rejection, necessitated by the amendment to independent claim 30 and the addition of new claims 62-64 in the reply filed 5/9/2011.

Barbas, III et al teach nucleic acid molecules encoding fusion proteins, expression vectors containing the nucleic acids, and cells containing the expression vectors, where the cells are plant cells (e.g., column 2, lines 18-24; column 3, lines 12-14). Further, Barbas, III et al teach compositions comprising the nucleic acid molecule and a pharmaceutically acceptable excipient (e.g., column 5, lines 49-56). Barbas, III et al teach that the fusion protein encoded by the nucleic acid molecule includes at least one DNA binding domain, at least one ligand binding domain, and at least one transcription modulating domain, and regulates expression by binding to a target sequence in a promoter (e.g., column 2, lines 59-67; column 5, line 66 to column 6, line 22; column 9, lines 56-60; column 17, lines 41-50; paragraph bridging columns 17-18). The transcription modulating domain may be a transcription activation domain (e.g., column 29, lines

30-34). In a preferred embodiment, the DNA binding domain includes at least three zinc finger modular units and binds to at least nine nucleotides (e.g., paragraph bridging columns 2-3; column 3, lines 59-64; paragraph bridging columns 20-21). For example, six zinc fingers will bind to a sequence of 18-bp (e.g., paragraph bridging columns 20-21). Barbas, III et al teach that it is advantageous to use zinc fingers, because of the ability to construct zinc fingers with unique specificity, which permits targeting and ligand-dependent control of expression of specific endogenous genes or exogenously administered genes (e.g., column 19, lines 28-35). Barbas, III et al teach that rules for creating synthetic zinc fingers with specificity to any desired target sequence are known (e.g., column 19, lines 36-49). Barbas, III et al teach that a zinc finger-nucleotide binding peptide domain contains a unique heptamer within the alpha-helical domain of the polypeptide, which heptameric sequence determines the binding specificity to the target nucleotide (e.g., column 20, lines 43-53). Further, Barbas, III et al teach that any framework sequences known in the art to function as part of a zinc finger protein can be modified to

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating cysteine residues separated by two amino acids and an alpha helix comprising one carboxy-terminal zinc coordinating histidine residue and one carboxy-terminal cysteine residue, where the carboxy-terminal histidine residue is amino terminal to the carboxy-terminal cysteine residue and the histidine and cysteine residues are separated by four amino acids, and where four amino acids are added C-terminal to the carboxy-terminal zinc coordinating residue.

Krizek et al teach that a large class of proteins has been discovered that is characterized by the presence of one or more sequences that closely approximate the form (Tyr,Phe)-X-Cys-$X_{2,4}$-Cys-X_3-Phe-X_5-Leu-X_2-His-$X_{3,4}$ where X represents relatively variable amino acids and where the structure fold into unique three-dimensional structures in the presence of metal ions (e.g., page 4518, left column, 1st paragraph). Krizek et al teach that the structure comprises a beta turn comprising two amino terminal zinc coordinating residues, and an alpha helix comprising two carboxy-terminal zinc coordinating residues (e.g., Figures 1 and 2). Krizek et al teach that a total of 131 sequences were known at the time their project was initiated, and the sequences are tabulated in Table 1 (e.g., page 4518, left column, 2nd paragraph). Krizek et al teach that examination of the sequence database revealed that six of the sequences lack the final histidine residue but have a cysteine residue within five amino acids of the conserved histidine (e.g., paragraph bridging pages 4521-4522). One such sequence is KYA**C**QV**C**HKSFSRMSLLNK**H**SSSN**C**TI from Drosophila Snail (e.g., Table 1). This sequence has two amino acids separating the two amino terminal zinc coordinating cysteine residues, and four amino acids separating the two carboxy-terminal zinc coordinating histidine and cysteine residues. Krizek et al teach that observation of zinc finger domains with a terminal cysteine suggested that cysteine could replace histidine as a metal-binding ligand from this position (e.g., paragraph bridging pages 4521-4522).

Boulay et al teach a polynucleotide encoding the KYA**C**QV**C**HKSFSRMSLLNK**H**SSSN**C**TI zinc finger of Drosophila Snail (e.g., Figure 3). Boulay et al teach that the Snail protein belongs to the class of regulatory proteins with DNA-binding activity (e.g., page 397, right column; paragraph bridging pages 397-398).

Because Barbas, III et al disclose nucleic acid molecules encoding a zinc finger protein comprising a zinc finger domain from any naturally occurring protein that has been used as a framework for modifying the DNA binding specificity according to known design rules, and Boulay et al teach a nucleic acid molecule encoding a zinc finger protein that binds DNA, it would have been obvious to one or ordinary skill in the art at the time the invention was made to include the framework sequence encoding the last finger (i.e., the CCHC zinc finger) of the Drosophila Snail protein, as shown by Krizek et al and Boulay et al, in the nucleic acid molecules of Barbas, III et al, where the finger of the Snail protein sequence has been modified to include a recognition helix that is engineered to bind the a target nucleic acid sequence taught by Barbas, III et al, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing the target nucleic acid sequence of Barbas, III et al. With respect to claims 28 and 54, which require the non-canonical zinc finger component to be the third zinc finger component or the first zinc finger component, respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the zinc fingers of Barbas III et al and Boulay et al in an order from N-terminus to C-terminus such that the non-canonical zinc fingers are present at the first and/or third zinc fingers. However, it is noted that the claims do not explicitly impose a linear order to the first, second and third zinc fingers. With respect to claims 62 and 63, the non-canonical zinc finger encoded by the polynucleotide based upon the Drosophila Snail framework would fall within the scope of the sequence of claim 62. Furthermore, Krizek et al teach that there are typically 3-4 amino acids C-terminal to the carboxy-terminal zinc coordinating residue, and Barbas, III et al teach linkage of zinc finger domains with a five amino acid TGEKP linker

(e.g., paragraph bridging columns 27-28). Thus, it would have been obvious to one of ordinary skill in the art to include 4 amino acids C-terminal to the carboxy-terminal zinc coordinating residue in order to provide a complete zinc finger domain linked to another zinc finger domain.

Furthermore, one would have been motivated to include the sequence encoding the CCHC type zinc fingers of Krizek et al and Boulay et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,329,728 B1; see the entire reference) in view of Barbas, III et al (US Patent No. 7,329,728 B1; see the entire reference) in view of Krizek et al (Journal of the American Chemical Society, Vol. 113, pages 4518-4523, 1991; see the entire reference), and Boulay et al (Nature, Vol. 330, pages 395-398, November 1987; see the entire reference) as applied to claims 25-28, 30-32, 36, 39-41, 53-57 and 62-64 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of claim 30 in the reply filed 5/9/2011.

The combined teachings of Barbas, III et al, Desjarlais et al, Krizek et al, and Roehm et al are described above and applied as before.

Barbas, III et al, Desjarlais et al, Krizek et al, and Roehm et al do not teach the polynucleotide where the activation domain is a maize C1 activation domain.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al because Barbas, III et al teach it is within the skill of the art to make a plant cell comprising the polynucleotide where the polynucleotide encodes a zinc finger-nucleotide binding polypeptide that activates expression of a gene operably linked to the target nucleotide sequence, and Guyer et al teach that the maize C1 activation domain functions in a plant cell to activate transcription from a heterologous DNA binding domain.

One would have been motivated to specifically use the maize C1 activation domain, because it was known in the art to function in plants. Based upon the teachings of the cited

references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 56 and 57 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2) in view of Filippova et al, Applicant's arguments filed 5/9/2011 have been fully considered but they are not persuasive.

The response asserts that the claim requires at least one residue between the two carboxy-terminal zinc coordinating residues to be altered as compared to a naturally occurring zinc finger. The response argues that neither Barbas nor Filippova teach such a modification.

These arguments are not found persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., alteration of at least one residue between the two carboxy-terminal zinc coordinating residues as compared to a naturally occurring zinc finger) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

The rejection of claims 25-28, 30-32, 36-37, 39-41 and 53-55 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2) in view of Filippova et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/9/2011.

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The rejection of claim 37 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,329,728 B1) in view of Filippova et al, and further in view of Guyer et al has been withdrawn in view of Applicant's amendment to the claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636